



Clinical trial results:

A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus GDC-0973 in Previously Untreated BRAF^{V600E} Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma

Summary

EudraCT number	2012-003008-11
Trial protocol	GB ES CZ AT NO DE BE SE IT NL HU FR
Global end of trial date	21 July 2019

Results information

Result version number	v4 (current)
This version publication date	16 July 2020
First version publication date	07 August 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GO28141
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01689519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	Medical Communications, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 April 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of vemurafenib in combination with cobimetinib (GDC-0973), compared with vemurafenib and placebo, in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma, as measured by progression-free survival (PFS), assessed by the study site investigator.

Protection of trial subjects:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 47
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 95
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	New Zealand: 10
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 29

Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	495
EEA total number of subjects	329

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	362
From 65 to 84 years	128
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Written informed consent for participation in the study was obtained before performing any study-specific screening tests or evaluations.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cobimetinib + Vemurafenib

Arm description:

Participants received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO518426
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vemurafenib 960 milligrams (mg) orally twice a day on Days 1-28 of each 28-day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	GDC-0973 RO5514041 XL518
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received cobimetinib 60 mg orally once daily on Days 1-21 of each 28-day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Arm title	Placebo + Vemurafenib
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Arm description:

Participants received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Arm type	Active comparator
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo orally once daily on Days 1-21 of each 28-day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest

Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	RO518426
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vemurafenib 960 milligrams (mg) orally twice a day on Days 1-28 of each 28-day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Number of subjects in period 1	Cobimetinib + Vemurafenib	Placebo + Vemurafenib
Started	247	248
Completed	0	0
Not completed	247	248
Adverse event, serious fatal	157	167
Physician decision	4	1
Consent withdrawn by subject	21	20
Unknown	2	4
Lost to follow-up	4	8
Study terminated by Sponsor	59	48

Baseline characteristics

Reporting groups

Reporting group title	Cobimetinib + Vemurafenib
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Reporting group description:

Participants received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group title	Placebo + Vemurafenib
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Reporting group description:

Participants received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group values	Cobimetinib + Vemurafenib	Placebo + Vemurafenib	Total
Number of subjects	247	248	495
Age Categorical			
Units:			
<=18 years	0	0	0
Between 18 and 65 years	183	179	362
>=65 years	64	69	133
Age Continuous			
Units: Years			
arithmetic mean	54.9	55.3	
standard deviation	± 14.0	± 13.8	-
Sex: Female, Male			
Units: Participants			
Female	101	108	209
Male	146	140	286
Race/Ethnicity, Customized			
Units: Subjects			
Asian	1	0	1
More than one race	1	1	2
Native Hawaiian or other Pacific Islande	0	1	1
Black or African American	0	0	0
White	227	235	462
Unknown or Not Reported	16	9	25
Other	2	2	4
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	14	12	26
Not Hispanic or Latino	213	223	436
Not Stated	16	10	26
Unknown	4	3	7

End points

End points reporting groups

Reporting group title	Cobimetinib + Vemurafenib
Reporting group description: Participants received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.	
Reporting group title	Placebo + Vemurafenib
Reporting group description: Participants received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.	

Primary: Progression-free survival

End point title	Progression-free survival
End point description: Progression-free survival was defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator using Response Evaluation Criteria in Solid Tumors v1.1, or death from any cause, whichever came first. Disease progression was defined as: (1) at least a 20% increase in the sum (the increase in the sum must be at least 5 mm) of diameters of target lesions, taking as reference the smallest sum during the study; (2) unequivocal progression of existing non-target lesions; or (3) the appearance of 1 or more new lesions.	
9999 = not estimable, could not be calculated due to too few events	
End point type	Primary
End point timeframe: Baseline to the 21 July 2019 data cut-off (up to 7 years, 6 months)	

End point values	Cobimetinib + Vemurafenib	Placebo + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)				
Primary Analysis: 9 May 2014	9.90 (9.00 to 9999)	6.20 (5.55 to 7.39)		
Post hoc Efficacy Analysis: 16 January 2015	12.30 (9.50 to 13.4)	7.20 (5.6 to 7.5)		
Extended 5-Year Analysis: 21 July 2019	12.60 (9.50 to 14.8)	7.20 (5.60 to 7.50)		

Statistical analyses

Statistical analysis title	Primary Analysis 9 May 2014
Statistical analysis description: The analysis was stratified by geographic region and metastasis classification (disease stage).	
Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib

Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.68

Statistical analysis title	Post hoc Efficacy Analysis: 16 January 2015
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Statistical analysis description:

The analysis was stratified by geographic region and metastasis classification (disease stage).

Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.72

Statistical analysis title	Extended 5-Year Analysis: 21 July 2019
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Statistical analysis description:

The analysis was stratified by geographic region and metastasis classification (disease stage).

Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.79

Secondary: Overall survival

End point title	Overall survival
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End point description:

Overall survival was defined as the time from randomization until the date of death from any cause.

0000 = not estimable, could not be calculated due to too few events

9999 = not estimable, could not be calculated due to too few events

End point type	Secondary
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End point timeframe:

Baseline to the 21 July 2019 data cut-off (up to 7 years, 6 months)

End point values	Cobimetinib + Vemurafenib	Placebo + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Months				
median (confidence interval 95%)				
Primary Analysis 9 May 2014	9999 (0000 to 9999)	9999 (0000 to 9999)		
Post hoc Analysis 16 January 2015	9999 (20.70 to 9999)	17.00 (15.00 to 9999)		
Final Analysis 28 August 2015	22.30 (20.30 to 9999)	17.40 (15.00 to 19.80)		
Extended 5-year Analysis 21 July 2019	22.50 (20.30 to 28.80)	17.40 (15.00 to 19.80)		

Statistical analyses

Statistical analysis title	Primary Analysis 9 May 2014
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Statistical analysis description:

The analysis was stratified by geographic region and metastasis classification (disease stage).

Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
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Number of subjects included in analysis	495
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Analysis specification	Pre-specified
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Analysis type	
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P-value	= 0.0463
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Method	Logrank
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Parameter estimate	Hazard ratio (HR)
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Point estimate	0.645
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.42
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upper limit	1
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Statistical analysis title	Post hoc Analysis 16 January 2015
Statistical analysis description: The analysis was stratified by geographic region and metastasis classification (disease stage).	
Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0034
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.87

Statistical analysis title	Final Analysis 28 August 2015
Statistical analysis description: The analysis was stratified by geographic region and metastasis classification (disease stage).	
Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.9

Secondary: Percentage of participants with an objective response

End point title	Percentage of participants with an objective response
End point description: An objective response was defined as a complete response or a partial response determined on two consecutive occasions ≥ 4 weeks apart. Responses were determined by Response Evaluation Criteria in Solid Tumors v1.1. A complete response was defined as the disappearance of all target lesions or the disappearance of all non-target lesions and normalization of tumor marker level. A partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter of target lesions.	
End point type	Secondary

End point timeframe:

Baseline to the 21 July 2019 data cut-off (up to 7 years, 6 months)

End point values	Cobimetinib + Vemurafenib	Placebo + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	248		
Units: Percentage of participants				
number (confidence interval 95%)				
Primary Analysis: 9 May 2014	67.60 (61.40 to 73.40)	44.80 (38.50 to 51.12)		
Post hoc Efficacy Analysis: 16 January 2015	69.60 (63.50 to 75.30)	50.00 (43.60 to 56.40)		
Extended 5-Year Analysis: 21 July 2019	69.90 (63.49 to 75.31)	49.60 (43.21 to 55.99)		

Statistical analyses

Statistical analysis title	Primary Analysis: 9 May 2014
Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	22.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.1
upper limit	31.6

Statistical analysis title	Post hoc Efficacy Analysis: 16 January 2015
Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	19.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	11
upper limit	28.3

Statistical analysis title	Extended 5-Year Analysis: 21 July 2019
Comparison groups	Cobimetinib + Vemurafenib v Placebo + Vemurafenib
Number of subjects included in analysis	495
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.4
upper limit	28.7

Secondary: Duration of response

End point title	Duration of response
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End point description:

Duration of response was defined as the time from first occurrence of a documented confirmed objective response until the time of disease progression, as determined by investigator review of tumor assessments using Response Evaluation Criteria in Solid Tumors v1.1 or death from any cause during the study. Disease progression was defined as: (1) at least a 20% increase in the sum (the increase in the sum must be at least 5 mm) of diameters of target lesions, taking as reference the smallest sum during the study; (2) unequivocal progression of existing non-target lesions; or (3) the appearance of 1 or more new lesions.

9999 = not estimable, could not be calculated due to too few events

End point type	Secondary
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End point timeframe:

Baseline to the 21 July 2019 data cut-off (up to 7 years, 6 months)

End point values	Cobimetinib + Vemurafenib	Placebo + Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	111		
Units: Months				
median (confidence interval 95%)				
Primary Analysis: 9 May 2014	9999 (9.30 to 9999)	7.29 (5.78 to 9999)		
Extended 5-Year Analysis: 21 July 2019	14.65 (12.9 to 19.3)	9.23 (7.50 to 12.90)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety data cut-off: July 2019; up to 7 years, 6 months

Adverse event reporting additional description:

Safety population: All participants who received at least 1 dose of study treatment (ie, cobimetinib/placebo or vemurafenib).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Cobimetinib + Vemurafenib
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Reporting group description:

Participants received cobimetinib 60 mg orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Reporting group title	Placebo + Vemurafenib
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Reporting group description:

Participants received placebo orally once daily on Days 1-21 of each 28 day cycle plus vemurafenib 960 mg orally twice a day on Days 1-28 of each 28 day cycle until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurs earliest.

Serious adverse events	Cobimetinib + Vemurafenib	Placebo + Vemurafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	105 / 248 (42.34%)	71 / 245 (28.98%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACANTHOMA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BENIGN NEOPLASM			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOMETRIAL ADENOCARCINOMA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL TRACT ADENOMA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KAPOSI'S SARCOMA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
KERATOACANTHOMA			
subjects affected / exposed	0 / 248 (0.00%)	4 / 245 (1.63%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 248 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA IN SITU			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCINOUS BREAST CARCINOMA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAPILLOMA			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR PAIN			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSIVE CRISIS			
subjects affected / exposed	2 / 248 (0.81%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBGALEAL HAEMATOMA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULITIS			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS LIMB			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
FATIGUE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAIT DISTURBANCE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SWELLING			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	7 / 248 (2.82%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	6 / 9	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	3 / 248 (1.21%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARCOIDOSIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
CERVICAL POLYP			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DYSPNOEA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 248 (0.00%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	3 / 248 (1.21%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
MANIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 248 (1.61%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 248 (1.21%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROCARDIOGRAM T WAVE ABNORMAL			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	3 / 248 (1.21%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOGLOBIN DECREASED			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIPASE INCREASED			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIVER FUNCTION TEST INCREASED			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FACIAL BONES FRACTURE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FRACTURE DISPLACEMENT			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVERDOSE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			

subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN LACERATION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC HAEMATOMA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	4 / 248 (1.61%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 8	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIAC FAILURE			

subjects affected / exposed	1 / 248 (0.40%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 248 (0.00%)	4 / 245 (1.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMA			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DIZZINESS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSARTHRIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSGEUSIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARALYSIS			
subjects affected / exposed	2 / 248 (0.81%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL PARESIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED TONIC-CLONIC SEIZURE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
HEADACHE			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDROCEPHALUS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYASTHENIA GRAVIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARAESTHESIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYNEUROPATHY			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	3 / 248 (1.21%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBARACHNOID HAEMORRHAGE			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CHORIORETINOPATHY			
subjects affected / exposed	3 / 248 (1.21%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRIDOCYCLITIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL DETACHMENT			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINAL HAEMORRHAGE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEROUS RETINAL DETACHMENT			
subjects affected / exposed	2 / 248 (0.81%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UVEITIS			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APHTHOUS ULCER			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	3 / 248 (1.21%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ANTRAL VASCULAR ECTASIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL PAIN			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OBSTRUCTION GASTRIC			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			

subjects affected / exposed	1 / 248 (0.40%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIODONTAL DISEASE			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL POLYP			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	3 / 248 (1.21%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	2 / 248 (0.81%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 248 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS ACUTE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

DERMATITIS EXFOLIATIVE GENERALISED			
subjects affected / exposed	0 / 248 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYTHEMA MULTIFORME			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYTHEMA NODOSUM			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERKERATOSIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANNICULITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	4 / 248 (1.61%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

RASH GENERALISED			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULAR			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULO-PAPULAR			
subjects affected / exposed	3 / 248 (1.21%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MORBILLIFORM			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URTICARIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	3 / 248 (1.21%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC NEPHROPATHY			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL COLIC			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETEROLITHIASIS			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BURSITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

MYALGIA			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYARTHRITIS			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHABDOMYOLYSIS			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABDOMINAL SEPSIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ABSCESS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS BACTERIAL			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
CLOSTRIDIUM DIFFICILE INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOCCAL SEPSIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 248 (0.40%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	1 / 248 (0.40%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 248 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS CLOSTRIDIAL			

subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENITOURINARY TRACT INFECTION			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL BACTERIAL INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN ABSCESS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	6 / 248 (2.42%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	1 / 248 (0.40%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUBERCULOSIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 248 (0.81%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VULVAL CELLULITIS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	6 / 248 (2.42%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERNATRAEMIA			

subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 248 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	1 / 248 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cobimetinib + Vemurafenib	Placebo + Vemurafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	239 / 248 (96.37%)	236 / 245 (96.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	16 / 248 (6.45%)	6 / 245 (2.45%)	
occurrences (all)	33	6	
KERATOACANTHOMA			
subjects affected / exposed	5 / 248 (2.02%)	20 / 245 (8.16%)	
occurrences (all)	6	26	
MELANOCYTIC NAEVUS			
subjects affected / exposed	5 / 248 (2.02%)	17 / 245 (6.94%)	
occurrences (all)	5	26	
SEBORRHOEIC KERATOSIS			
subjects affected / exposed	15 / 248 (6.05%)	21 / 245 (8.57%)	
occurrences (all)	15	24	

SKIN PAPILLOMA subjects affected / exposed occurrences (all)	18 / 248 (7.26%) 26	30 / 245 (12.24%) 36	
SQUAMOUS CELL CARCINOMA OF SKIN subjects affected / exposed occurrences (all)	10 / 248 (4.03%) 25	33 / 245 (13.47%) 66	
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	50 / 248 (20.16%) 60	30 / 245 (12.24%) 33	
General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all)	51 / 248 (20.56%) 96	43 / 245 (17.55%) 50	
CHILLS subjects affected / exposed occurrences (all)	25 / 248 (10.08%) 28	14 / 245 (5.71%) 17	
FATIGUE subjects affected / exposed occurrences (all)	93 / 248 (37.50%) 137	83 / 245 (33.88%) 99	
OEDEMA PERIPHERAL subjects affected / exposed occurrences (all)	38 / 248 (15.32%) 49	28 / 245 (11.43%) 32	
PYREXIA subjects affected / exposed occurrences (all)	77 / 248 (31.05%) 130	60 / 245 (24.49%) 77	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	28 / 248 (11.29%) 36	32 / 245 (13.06%) 37	
DYSPNOEA subjects affected / exposed occurrences (all)	19 / 248 (7.66%) 26	19 / 245 (7.76%) 23	
OROPHARYNGEAL PAIN			

subjects affected / exposed occurrences (all)	19 / 248 (7.66%) 20	22 / 245 (8.98%) 28	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	16 / 248 (6.45%)	11 / 245 (4.49%)	
occurrences (all)	18	12	
DEPRESSION			
subjects affected / exposed	15 / 248 (6.05%)	11 / 245 (4.49%)	
occurrences (all)	17	11	
INSOMNIA			
subjects affected / exposed	19 / 248 (7.66%)	27 / 245 (11.02%)	
occurrences (all)	24	31	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	65 / 248 (26.21%)	44 / 245 (17.96%)	
occurrences (all)	94	48	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	64 / 248 (25.81%)	29 / 245 (11.84%)	
occurrences (all)	87	30	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	46 / 248 (18.55%)	26 / 245 (10.61%)	
occurrences (all)	67	30	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	20 / 248 (8.06%)	17 / 245 (6.94%)	
occurrences (all)	29	22	
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	16 / 248 (6.45%)	10 / 245 (4.08%)	
occurrences (all)	19	10	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	90 / 248 (36.29%)	10 / 245 (4.08%)	
occurrences (all)	171	13	
BLOOD CREATININE INCREASED			
subjects affected / exposed	45 / 248 (18.15%)	20 / 245 (8.16%)	
occurrences (all)	59	25	

BLOOD LACTATE DEHYDROGENASE INCREASED	subjects affected / exposed	15 / 248 (6.05%)	8 / 245 (3.27%)	
	occurrences (all)	30	8	
EJECTION FRACTION DECREASED	subjects affected / exposed	31 / 248 (12.50%)	12 / 245 (4.90%)	
	occurrences (all)	46	13	
ELECTROCARDIOGRAM QT PROLONGED	subjects affected / exposed	12 / 248 (4.84%)	13 / 245 (5.31%)	
	occurrences (all)	15	19	
GAMMA-GLUTAMYLTRANSFERASE INCREASED	subjects affected / exposed	57 / 248 (22.98%)	45 / 245 (18.37%)	
	occurrences (all)	82	61	
WEIGHT DECREASED	subjects affected / exposed	18 / 248 (7.26%)	14 / 245 (5.71%)	
	occurrences (all)	20	17	
Injury, poisoning and procedural complications				
SUNBURN	subjects affected / exposed	37 / 248 (14.92%)	45 / 245 (18.37%)	
	occurrences (all)	60	68	
Nervous system disorders				
DIZZINESS	subjects affected / exposed	18 / 248 (7.26%)	7 / 245 (2.86%)	
	occurrences (all)	18	8	
DYSGEUSIA	subjects affected / exposed	27 / 248 (10.89%)	16 / 245 (6.53%)	
	occurrences (all)	29	17	
HEADACHE	subjects affected / exposed	50 / 248 (20.16%)	41 / 245 (16.73%)	
	occurrences (all)	76	50	
Blood and lymphatic system disorders				
ANAEMIA	subjects affected / exposed	51 / 248 (20.56%)	21 / 245 (8.57%)	
	occurrences (all)	76	26	
Eye disorders				

CHORIORETINOPATHY			
subjects affected / exposed	30 / 248 (12.10%)	4 / 245 (1.63%)	
occurrences (all)	36	9	
VISION BLURRED			
subjects affected / exposed	32 / 248 (12.90%)	8 / 245 (3.27%)	
occurrences (all)	37	9	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	30 / 248 (12.10%)	20 / 245 (8.16%)	
occurrences (all)	37	23	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	15 / 248 (6.05%)	18 / 245 (7.35%)	
occurrences (all)	17	21	
CONSTIPATION			
subjects affected / exposed	27 / 248 (10.89%)	29 / 245 (11.84%)	
occurrences (all)	37	31	
DIARRHOEA			
subjects affected / exposed	151 / 248 (60.89%)	84 / 245 (34.29%)	
occurrences (all)	311	162	
DYSPEPSIA			
subjects affected / exposed	19 / 248 (7.66%)	13 / 245 (5.31%)	
occurrences (all)	22	15	
NAUSEA			
subjects affected / exposed	108 / 248 (43.55%)	67 / 245 (27.35%)	
occurrences (all)	184	83	
STOMATITIS			
subjects affected / exposed	17 / 248 (6.85%)	3 / 245 (1.22%)	
occurrences (all)	27	3	
VOMITING			
subjects affected / exposed	69 / 248 (27.82%)	33 / 245 (13.47%)	
occurrences (all)	108	42	
Skin and subcutaneous tissue disorders			
ACTINIC KERATOSIS			
subjects affected / exposed	13 / 248 (5.24%)	27 / 245 (11.02%)	
occurrences (all)	32	31	
ALOPECIA			

subjects affected / exposed	42 / 248 (16.94%)	75 / 245 (30.61%)
occurrences (all)	44	78
DRY SKIN		
subjects affected / exposed	37 / 248 (14.92%)	42 / 245 (17.14%)
occurrences (all)	40	46
DERMATITIS ACNEIFORM		
subjects affected / exposed	37 / 248 (14.92%)	22 / 245 (8.98%)
occurrences (all)	47	26
ERYTHEMA		
subjects affected / exposed	32 / 248 (12.90%)	36 / 245 (14.69%)
occurrences (all)	56	57
HYPERKERATOSIS		
subjects affected / exposed	31 / 248 (12.50%)	74 / 245 (30.20%)
occurrences (all)	39	130
KERATOSIS PILARIS		
subjects affected / exposed	13 / 248 (5.24%)	26 / 245 (10.61%)
occurrences (all)	14	30
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME		
subjects affected / exposed	18 / 248 (7.26%)	9 / 245 (3.67%)
occurrences (all)	23	10
PHOTOSENSITIVITY REACTION		
subjects affected / exposed	86 / 248 (34.68%)	48 / 245 (19.59%)
occurrences (all)	119	58
PRURITUS		
subjects affected / exposed	51 / 248 (20.56%)	48 / 245 (19.59%)
occurrences (all)	85	54
RASH		
subjects affected / exposed	101 / 248 (40.73%)	97 / 245 (39.59%)
occurrences (all)	158	121
RASH MACULO-PAPULAR		
subjects affected / exposed	37 / 248 (14.92%)	37 / 245 (15.10%)
occurrences (all)	61	47
SOLAR DERMATITIS		
subjects affected / exposed	18 / 248 (7.26%)	14 / 245 (5.71%)
occurrences (all)	34	23

Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	96 / 248 (38.71%)	105 / 245 (42.86%)	
occurrences (all)	172	179	
BACK PAIN			
subjects affected / exposed	21 / 248 (8.47%)	15 / 245 (6.12%)	
occurrences (all)	30	15	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	17 / 248 (6.85%)	16 / 245 (6.53%)	
occurrences (all)	18	19	
MYALGIA			
subjects affected / exposed	41 / 248 (16.53%)	33 / 245 (13.47%)	
occurrences (all)	53	37	
PAIN IN EXTREMITY			
subjects affected / exposed	32 / 248 (12.90%)	40 / 245 (16.33%)	
occurrences (all)	51	54	
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	18 / 248 (7.26%)	8 / 245 (3.27%)	
occurrences (all)	19	10	
FOLLICULITIS			
subjects affected / exposed	19 / 248 (7.66%)	12 / 245 (4.90%)	
occurrences (all)	22	15	
NASOPHARYNGITIS			
subjects affected / exposed	23 / 248 (9.27%)	18 / 245 (7.35%)	
occurrences (all)	29	21	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	14 / 248 (5.65%)	11 / 245 (4.49%)	
occurrences (all)	18	15	
URINARY TRACT INFECTION			
subjects affected / exposed	17 / 248 (6.85%)	11 / 245 (4.49%)	
occurrences (all)	25	13	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	55 / 248 (22.18%)	50 / 245 (20.41%)	
occurrences (all)	75	55	

HYPONATRAEMIA			
subjects affected / exposed	13 / 248 (5.24%)	3 / 245 (1.22%)	
occurrences (all)	19	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2014	Changes that allow for symmetry in the treatment of patients receiving rituximab or obinutuzumab in case of hepatitis B reactivation. Changes to clarify that either antibody should be held in case of serious infection. clarification that patients with mantle cell lymphoma (MCL) and small lymphocytic lymphoma (SLL) were not eligible for the dose escalation portion of the study for safety reasons.
23 May 2014	Changes amended following identification of higher incidence of thrombocytopenia and hemorrhagic events in patients receiving obinutuzumab. Guidelines for management of patients with thrombocytopenia, especially during the first cycle have been added.
01 October 2014	An exploratory analysis of minimal residual disease has been added. Language has been added indicating the possibility of continued cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment for up to eight cycles in selected patients who are tolerating therapy well and for whom it is felt by the investigator to be appropriate. Response criteria have been updated to be consistent with the 2014 Lugano Classification. Safety language has been updated.
24 April 2015	GDC-0199 dosing schedule updated. Characterization of the pharmacokinetics of the cyclophosphamide, doxorubicin and vincristine (CHO) components was deleted from the Pharmacokinetic Objectives as detailed characterization cannot be achieved with the current PK sampling scheme.
07 December 2015	An interim safety analysis has been added after 20 patients in the R-CHOP arm in the Phase II portion of the study have completed two cycles of treatment in order to confirm the safety and tolerability of the combination therapy at the venetoclax. The primary objectives of Phase II of the study have been modified to include assessment of efficacy of R-CHOP+ Venetoclax in patients with co-expression of both Bcl-2 and c-Myc. The term PET/CT will be replaced with PET-CT throughout the protocol.
10 October 2016	Venetoclax nonclinical toxicology section updated based on recent data findings. Twelve month Progression Free Survival (PFS) was added as a secondary efficacy objective. Information was added regarding the decision to not open Arm B in Phase II in DLBCL on the basis of information from the GOYA study results.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30850381>